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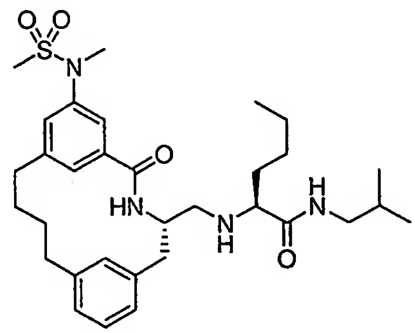
(54) Title: MACROCYCLIC BETA-SECRETASE INHIBITORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

(57) Abstract: The present invention is directed to compounds which are inhibitors of the beta-secretase enzyme and that are useful in the treatment or prevention of diseases in which the beta-secretase enzyme is involved, such as Alzheimer's disease. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the beta-secretase enzyme is involved.

understood. These examples are illustrative only and should not be construed as limiting the invention in any way. ^{1}H NMR was obtained on a spectrometer running at 400 MHz.

EXAMPLE 1



Step A: To 3-Nitrobenzoate (35.3 g, 195 mmol) in trifluoromethane sulfonic acid (100 mL) at 0°C was added N-iodosuccinimide (43.8 g, 195 mmol) portionwise. The ice bath was removed and stirring was continued at ambient temperature for 48 hrs. The reaction mixture was cooled to 0°C and quenched with water (500 mL). The mixture was extracted three times with EtOAc (250 mL) and the combined extracts were washed with a 10% $NaHSO_3$ solution. The organics were dried over $MgSO_4$, concentrated, and purified on silica gel (10% EtOAc in Hex) affording the intermediate. ^{1}H NMR ($CDCl_3$) δ 8.81 (s, 1H), 8.73 (s, 1H), 8.68 (s, 1H), 4.00 (s, 3H).

Step B: Tin chloride (88.6 g, 392 mmol) in EtOH (50 mL) was refluxed and a 1:1 THF:EtOH (100 mL) solution of the nitrobenzoate from step A (24.1 g, 78.4 mmol)was added dropwise. The reaction mixture was refluxed for 30 minutes then cooled to 0°C. The solution was basified to pH 8-9 with aq. Na_2CO_3. The aqueous layer was extracted with EtOAc (3 x 700 mL). The combined organics were washed with saturated $NaHCO_3$ then brine. The organics were dried over Na_2SO_4 and concentrated affording the crude aniline. LCMS [M + H] = 278.0

Step C: To a 0°C solution of the aniline from step B (21.7 g, 78.3 mmol) in 3:1 CH_2Cl_2:pyridine (75 mL) was added methanesulfonyl chloride(6.36 mL, 82.2 mmol). The ice bath was removed after 15 minutes and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (200 mL), washed 2x 1N HCl, and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (1:1 EtOAc/Hexanes) to provide he

sulfonamide. LCMS [M^+] 355.8. ^1H NMR ($CDCl_3$) δ 8.17 (s, 1H), 7.86 (s, 1H), 7.18 (s, 1H), 3.95 (s, 3H), 3.08 (s,3H).

Step D: NaH (0.49 g, 12.30 mmol, 60 % oil dispersion) was added to a solution of the sulfonamide from step C (3.12 g, 8.79 mmol), and methyl iodide (1.75 g, 12.3 mmol) in DMF (20 mL). The reaction was stirred at 50°C for 2 hours afterwhich the reaction was quenched with saturated NH_4Cl and extracted with EtOAc (3 x 100 mL). The combined organics were washed with water (2 x 100 mL), brine (1 x 50 mL) and dried of $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (25% EtOAc/Hexanes) to provide the N- methlysulfonamide. LCMS [M^+]: 369.9. ^1H NMR ($CDCl_3$) δ 8.29 (s, 1H), 7.96 (s, 2H), 3.93 (s, 3H), 3.34 (s, 3H), 2.88 (s, 3H)

Step E: A DMF solution (20 mL) of iodide from step D (3.15 g, 8.54 mmol) and allyltributyl stannane (3.39 g, 10.24 mmol) was degassed with a stream of argon for 15 minutes. To the degassed solution was added $Pd(PPh_3)_4$ (0.99 g, 0.85 mmol) afterwhich the reaction mixture was heated to 80°C for 2 h. The solution was cooled, diluted with H_2O (250 mL), and extracted with EtOAc (3 x 100 mL).). The combined organic layers were washed with water (2 x 100 mL), brine (1 x 50 mL), and dried of $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (40% EtOAc/Hexanes) to provide the allylated product.
LCMS [M+H]: 284.1. ^1H NMR ($CDCl_3$) δ 7.84 (s, 1H), 7.82 (s, 1H), 7.47 (s, 1H), 5.97 (m, 1H), 5.14 (m, 2H), 3.93 (s, 3H), 3.46 (d, J = 6.7 Hz, 2H), 3.36 (s, 3H), 2.87 (s, 3H).

Step F: To the ester from step E (1.79 g, 6.34 mmol) in 40 mL THF:MeOH (1:1) was added 2N NaOH (9.51 mL, 19.0 mmol). The solution was heated to 50°C for 1 h. The reaction mixture was concentrated, acidified with 1N HCl (50 mL), and extracted with EtOAc (3 x 50mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the desired carboxylic acid. LCMS [M+H] = 270.2

Step G: A solution containing the carboxylic acid from step F (1.38 g, 5.13 mmol), *m*-allyl tyrosine methyl ester HCl (see Tilley et al., *J Med Chem* 1991 (34) (3) 1125-1136 for analogous preparation) (1.31 g, 5.13 mmol) BOP reagent (2.27 g, 5.39 mmol), and diisopropyl ethylamine (2.68 mL, 15.39 mmol) was stirred at rt for 1 h in 100 mL of DCM. The solvent was evaporated and the residue was purified by silica gel chromatography (1:1 EtOAc/Hexanes) to afford the desired amide as a light yellow oil. LCMS [M+H] = 471.1. ^1H NMR ($CDCl_3$) δ 7.60 (s, 1H), 7.40 (s, 1H), 7.38 (s, 1H), 7.23 (t, J = 7.6

Hz, 1H), 7.10 (d, J = 7.3 Hz, 1H), 6.98 (d, J = 11 Hz, 1H), 6.96 (s, 1H), 6.55 (d, J = 7.2 Hz, 1H), 5.98-5.86 (m ,2H), 5.15-5.01 (m, 4H), 3.77 (s, 3H), 3.42 (d, J = 6.4 Hz, 2H), 3.34 (d, J = 7.0 Hz, 2H), 3.33 (s, 3H), 3.23 (dd, J = 8.3, 5.8 Hz, 2H), 2.84 (s, 3H).

Step H: 2.17 g (4.61 mmol) of the diene from step G was dissolved in DCM (2 L) and degassed with a steam of argon for 15 min. Tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazo[-2-ylidine][benzylidine]ruthenium(IV)dichloride (0.42 g, 0.49 mmol) was added and the reaction mixture was heated to 50°C for 30 min. The reaction was cooled, DMSO (1 mL) was added and the reaction was stirred at rt for 12 h. The solvent was evaporated and the residue was purified by silica gel chromatography (80% EtOAc/ Hexanes) to provide the desired macrocycle as a single geometric isomer. LCMS [M+H] = 443.0. ^{1}H NMR ($CDCl_3$) δ 7.64 (s, 2H), 7.47 (s, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.20 (s, 1H), 7.18 (d, J = 9.3 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 6.40 (d, J = 9.0 Hz, 1H), 5.73 (m, 2H), 5.09 (m, 1H), 3.80 (s, 3H), 3.52-3.23 (m, 5H), 3.32 (s, 3H), 3.04 (dd, J = 13, 5.4 Hz, 1H), 2.83 (s, 3H).

Step I: A solution of the macrocyclic alkene from step H in 50 mL of MeOH was treated with a catalytic amount of 10% Pd/C and stirred at rt under a hydrogen atmosphere for 2 h. The reaction was filtered through a pad of celite and the solvent was removed *in vacuo* to provide the reduced macrocycle as a white foam. LCMS [M+H] = 445.26. ^{1}H NMR ($CDCl_3$) δ 7.59 (s, 1H), 7.38 (s, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.05 (s, 1H), 6.96 (d, J = 7.5 Hz, 1H), 6.83 (s, 1H), 6.19 (d, J = 8.0 Hz, 1H), 4.99 (dd, J = 12, 5.7 Hz, 1H), 3.86 (s, 3H), 3.31 (s, 3H), 3.29 (m ,1H), 3.18 (dd, J = 14, 6.0 Hz, 1H), 2.84 (m ,2H), 2.83 (s, 3H), 2.72 (dd, J = 18, 6.5 Hz, 1H), 2.59 (t, J = 11 Hz, 1H), 1.81-1.58 (m, 4H).

Step J: A solution containing the reduced alkene from step I (1.05 g, 2.36 mmol) in THF (30 mL) was treated with $LiBH_4$ (2.0M THF solution, 3.54 mL, 7.08 mmol). The reaction mixture was heated to 50°C for 1h. The reaction was quenched by the addition of cold methanol. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (5% methanol/chlorform) to provide the desired alcohol as a white foam. LCMS [M+H] = 417.1. ^{1}H NMR ($CDCl_3$) δ 7.54 (s, 1H), 7.37-7.33 (m, 2H), 7.19-7.16 (m, 2H), 7.08 (s, 1H), 6.51 (s, 1H), 6.18 (d, J = 4.0 Hz, 1H), 4.03 (m, 1H), 3.90 (dd, J = 11, 2.9 Hz, 1H), 3.80 (dd, J = 11, 7.3 Hz, 1H), 3.29 (s, 3H), 3.12 (dd, J = 13, 4.9 Hz, 1H), 2.89 (dd, J = 13, 4.9 Hz, 1H), 2.83 (s, 3H), 2.83 (m, buried, 1H), 2.75-2.66 (m, 2H), 2.59-2.53 (m, 1H)m 1.83-1.64 (m, 4H).

Step K: A solution containing the alcohol from step J (0.143 g, 0.343 mmol) in 4 mL DMSO:DCM (3:1) was treated with triethylamine (0.17 g, 1.71 mmol) then SO_3-pyridine complex (0.21 g, 1.37 mmol). The reaction mixture was stirred at rt for 1 h. The solution was diluted with H_2O (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with 1N HCl (2 x 50 mL) and brine (1 x 50 mL) then dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo* to afford the desired aldehyde. LCMS [M+H] = 415.1.

Step L: A solution containing the aldehyde from step K (0.040 g, 0.096 mmol) and N-isobutyl-L-norleucinamide HCl (0.064 g, 0.289 mmol) in 5 mL MeOH was treated with $NaCNBH_3$ (0.018 g, 0.289 mmol) and stirred at rt for 12 h. The solvent was evaporated and the residue was purified by reverse phase HPLC to afford the title compound. LCMS [M+H] = 585.2. ^{1}H NMR (CD_3OD) δ 7.47 (s, 1H), 7.35 (s, 1H), 7.30 (t, J = 7.3, 1H), 7.30 (s, 1H), 7.20 (d, J = 8.1 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.60 (s, 1H), 4.29 (m, 1H), .391 (t, J = 6.5 Hz, 1H), 3.41-3.27 (m, 2H), 3.27 (s, 3H), 3.25 (m, 2H), 3.04 (dd, J = 13, 6.9 Hz, 1H), 2.89 (m, 1H), 2.87 (s, 3H), 2.75 (m, 2H), 2.52 (m, 1H), 1.93-1.64 (m, 9H), 1.43 (m, 3H), 0.96 (d, J = 6.7 Hz, 6H), 0.96 (t, buried, 3H).

The following compounds were prepared in a manner similar to the compounds of the foregoing schemes and examples using appropriate starting materials and reagents.

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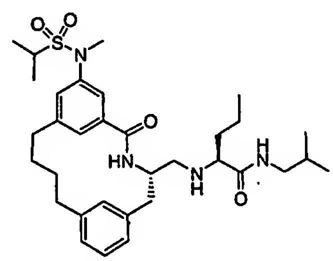
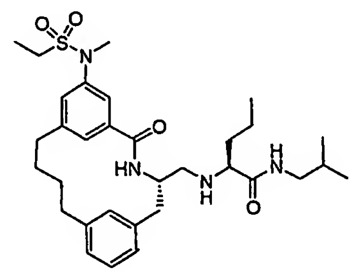
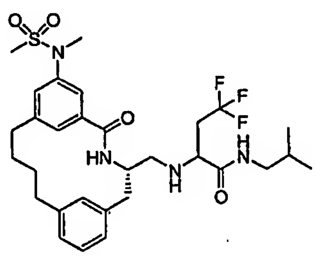
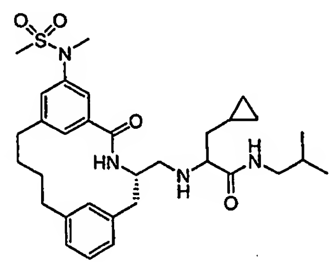
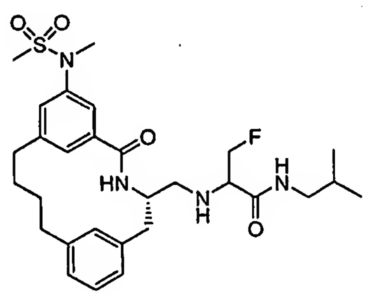
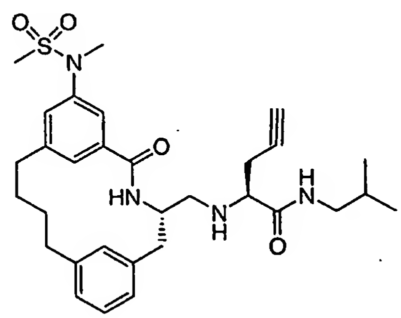
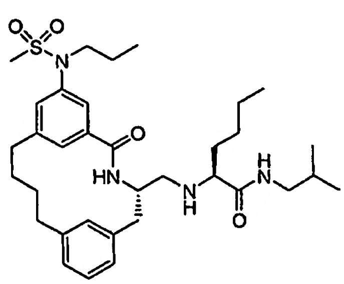
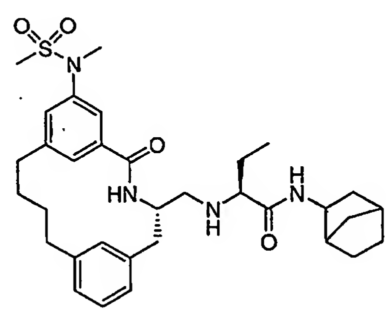
2		3	
4		5	
6		7	
8		9	

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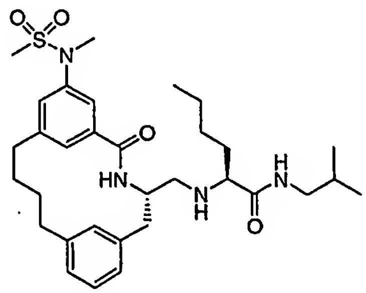
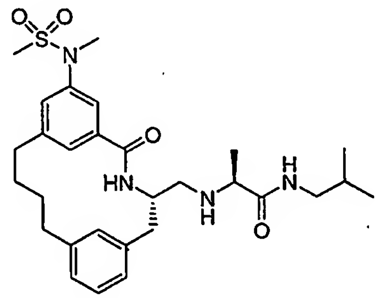
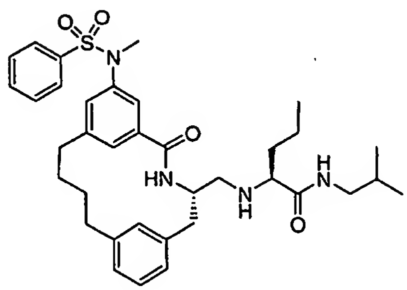
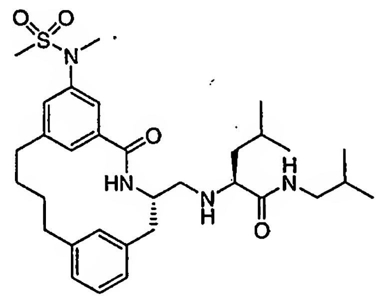
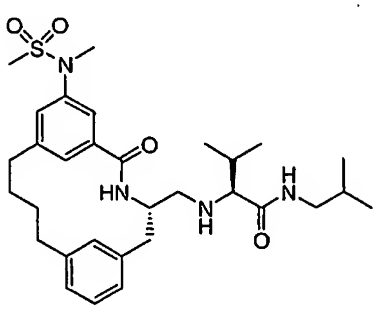
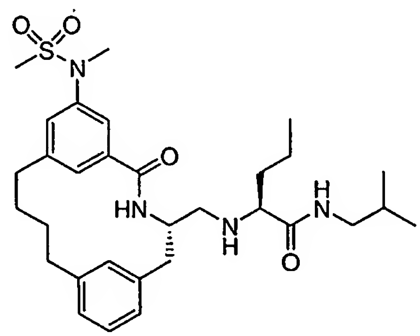
10		11	
12		13	
14		15	

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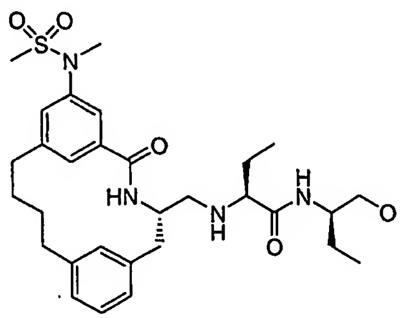
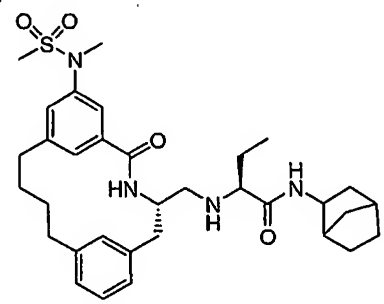
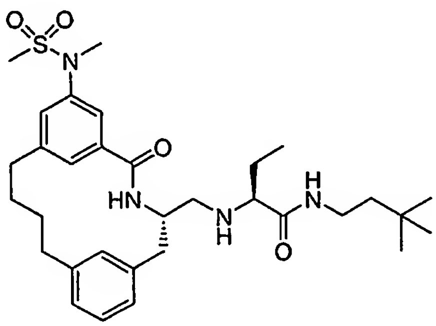
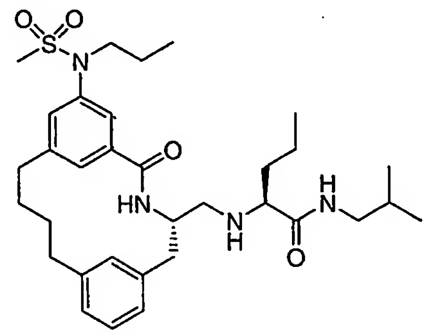
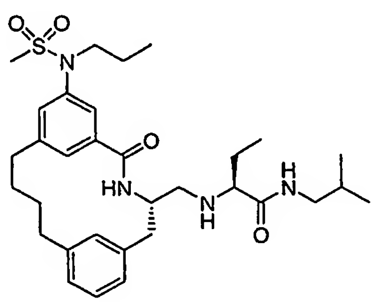
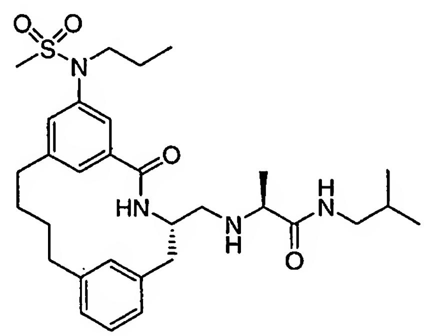
16		17	
18		19	
20		21	

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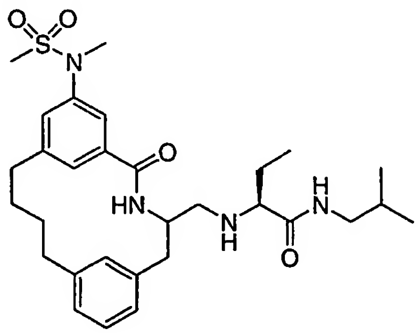
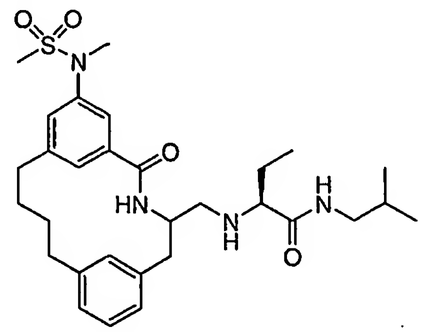
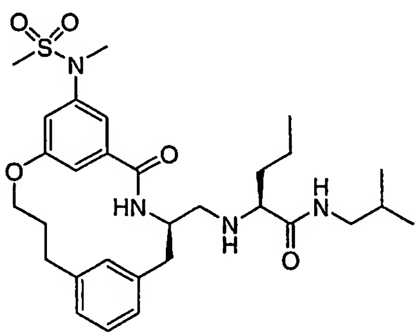
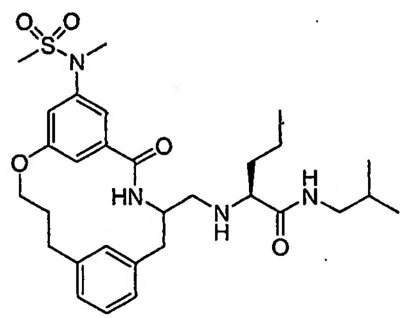
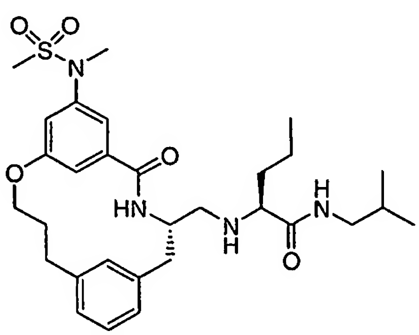
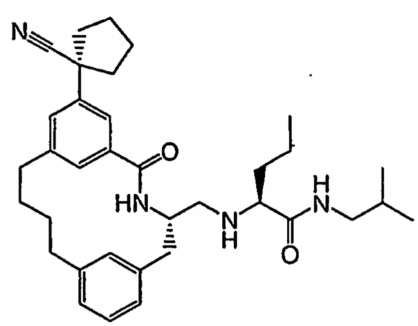
22		23	
24		25	
26		27	

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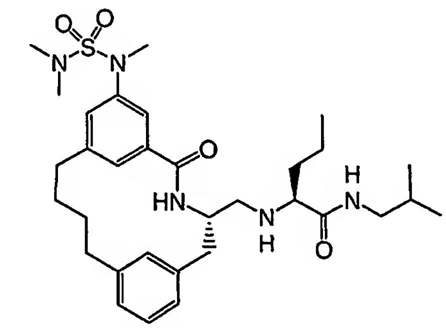
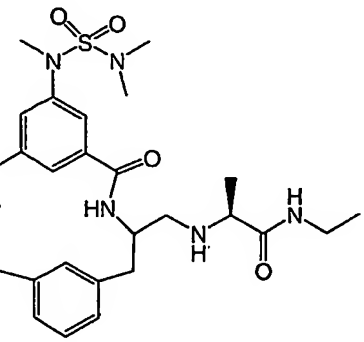
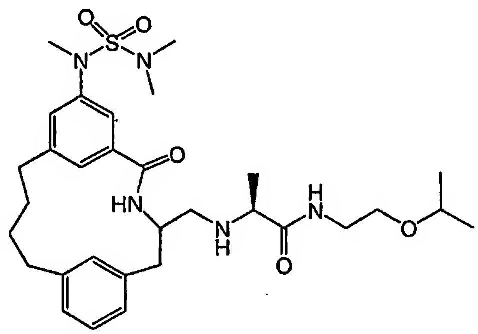
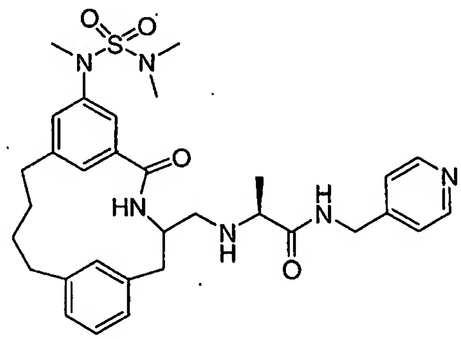
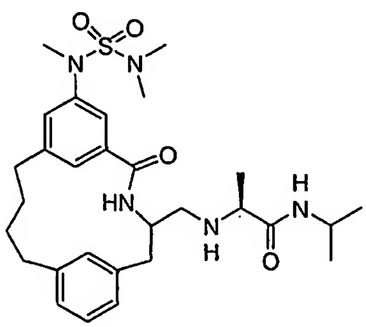
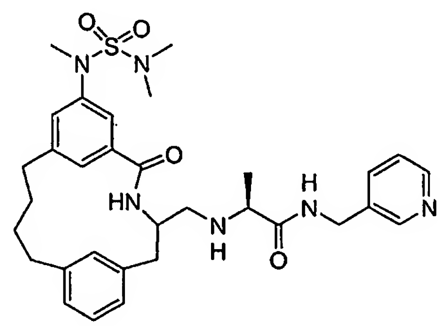
28		29	
30		31	
32		33	

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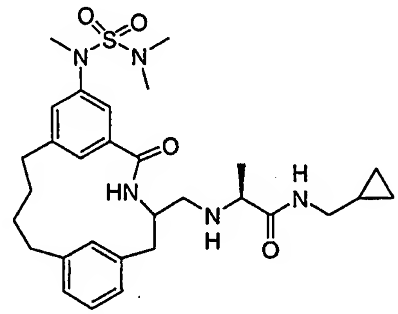
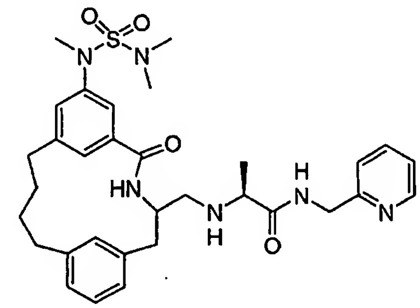
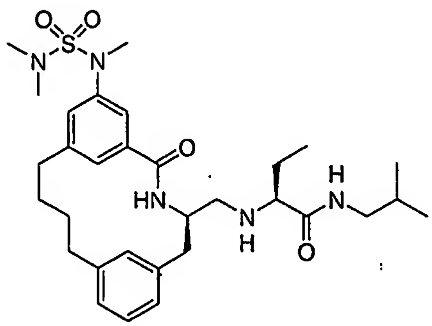
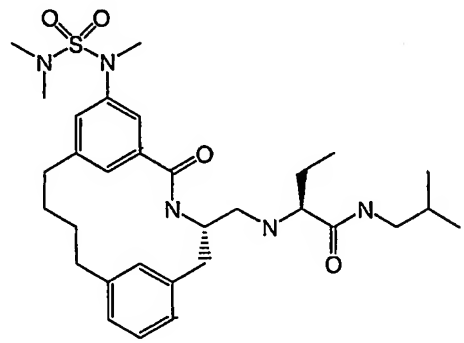
34		35	
36		37	

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.